Infective Endocarditis—A 25 Year Overview of Diagnosis and Therapy

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Diagnosis and management of infective endocarditis have significantly changed in the past 25 years. Improved bacteriologic techniques have allowed detection of cases of infective endocarditis caused by unusual organisms. Bactericidal therapy has become available for patients with gram-negative endocarditis and antimicrobial therapy has improved. Echocardiography has become an important diagnostic and management aid, and cardiac valve replacement has dramatically improved the outlook for many patients.

Infective endocarditis was described by Morgagni in the mid 1700s (1). Rokitansky established its infectious etiology during the mid 1800s by identifying microbes within vegetations at embolic sites (2). In 1869, Winge demonstrated cocci in stained sections of lesions in patients with endocarditis (3). The bacterial etiology was established by Heiberg, Klebs and others (4–6).

On February 26, 1885, William Osler gave the first of three Gulstonian lectures on malignant endocarditis. He began, "It is of use, from time to time, to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future." In this and the following lectures on March 3 and March 5, 1885, Osler presented a remarkable amount of clinical and pathologic data on the disease he termed malignant endocarditis. The reader is referred to the recent informative scholarly observations of the Osler Gulstonian lectures (7,8).

Half a century elapsed between Osler's Gulstonian lectures in 1885 and the next major development in the history of the disease. In 1937 sulfonamides were introduced, and although the cure rate was low, these agents represented the first step in the specific treatment of infective endocarditis (9). Penicillin, introduced in 1944, was the first effective antimicrobial therapy for this disease (10–12).

It seems appropriate now, almost 100 years after the Gulstonian lectures and 25 years after the early antibiotic era, to note the changes that have occurred, and in particular the changes during the last quarter century. The changes involve the spectrum of etiologic organisms causing infective endocarditis, changes in clinical presentation, new complicating factors in disease causation, important additions to laboratory investigations, significant changes in medical antibiotic treatment and the addition of surgical treatment in selected patients. In addition, the mean age of patients has progressively increased from 40 to 42 years in the 1950s to 50 to 54 years in the 1960s, and the disease has become increasingly common in patients over 60 years of age (13,14).

Microbiologic Etiology of Infective Endocarditis

Improved microbiologic techniques. Virtually any organism is capable of causing infective endocarditis (15–20). Table 1 compares the microbiologic cause of infective endocarditis in 172 patients seen at the Mayo Clinic from 1951 through 1957 with that in 393 patients treated at the Mayo Clinic 20 years later. These data suggest that the microbiologic causes in the two periods differed. The increased number of reports of previously uncommon causes of infective endocarditis is probably attributable to two factors: 1) improved microbiologic techniques, and 2) a change in the microbiologic spectrum. The impact of improved microbiologic techniques is apparent in patients with gram-negative bacilli, "other" infections and "culture-negative" endocarditis. *Hemophilus parainfluenzae* is a member of the HACEK group of microorganisms, which are slow-grow-

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Table 1. Microbiologic Findings in Infective Endocarditis*

Finding	1951 to 1957 Patients (no.)	1951 to 1957 Patients (%)	1970 to 1979 Patients (no.)	1970 to 1979 Patients (%)
Viridans streptococci	91	53	149	39
Group D streptococci	28	16	79†	20
Staphylococcus aureus	24	14	72	18
S. epidermidis	4	2	16	4
Gram-negative bacilli	10	6	35	9
Other microorganisms	1	1	29	7
Negative blood cultures	14	8	13	3
Total	172	100	393	100

*From Wilson WR, Giuliani ER, Geraci JE. Treatment of penicillin-sensitive streptococcal infective endocarditis. Mayo Clin Proc 1982;57:81–5.
†Includes 26 *Streptococcus bovis* isolates.

ing, fastidious gram-negative bacilli with special growth requirements; the HACEK group includes *Hemophilus sp, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens* and *Kingella kingii*. These fastidious microorganisms constitute a major portion of the gram-negative bacillary causes of infective endocarditis in the later group of patients seen at the Mayo Clinic. A prolonged period of incubation, often 3 weeks or longer, is frequently necessary to detect growth of these microorganisms in blood cultures. Because of the fastidious growth requirements and prolonged incubation period, cases caused by the HACEK group of microorganisms during the 1950s were likely to have been classified as "culture-negative" endocarditis.

During the 1970s, approximately 8% of cases of penicillin-sensitive streptococcal infective endocarditis were caused by nutritionally variant viridans streptococci. These microorganisms require a pyridoxal-supplemented medium for growth. Cases of infective endocarditis caused by nutritionally variant viridans streptococci were also likely to have been classified as "culture-negative" during the 1950s. Of the 29 patients seen during the 1970s with infective endocarditis caused by "other" microorganisms, 8 had infections with anaerobic gram-positive cocci. In the 1950s, anaerobic microbiology was largely a research tool and patients with infective endocarditis caused by anaerobic bacteria would have been included in the "culture-negative" group.

Changing microbiologic spectrum. Although improved techniques may explain some of the microbiologic differences between infective endocarditis diagnosed during the 1950s and that of the 1970s, the experiences at the Mayo Clinic and elsewhere indicate that the bacterial spectrum of infective endocarditis is changing. The percent of patients at the Mayo Clinic with endocarditis caused by viridans streptococci declined from 53% during the 1950s to 38% in the 1970s. The average annual number of cases of infective endocarditis increased from 24.5 in the 1950s to 39 20 years later, and the number of patients with viridans streptococcal infections increased from 13 a year in the 1950s to 15 a year in the 1970s. It is clear that there are not fewer patients with viridans streptococcal endocarditis but rather more patients with endocarditis caused by other microorganisms. The change in the microbiologic spectrum is partly a result of nosocomially acquired infections associated with the increased use of intravascular prostheses and invasive mechanical life support and monitoring systems. Another major factor responsible for the change in the microbiologic spectrum is the increased number of patients with infective endocarditis related to the intravenous use of illicit drugs. Nosocomially acquired or addict-associated endocarditis is often caused by *Staphylococcus epidermidis*, gram-negative bacilli, Candida and "opportunistic" microorganisms—uncommon causes of infective endocarditis in the 1950s.

Role of Blood Cultures in the Diagnosis of Infective Endocarditis

Despite the changing spectrum of infective endocarditis, at least 75% of infections are caused by streptococci or staphylococci (15–20). During the 1950s, the majority of these cases were readily diagnosed by routine blood culture systems. Improvement in microbiologic techniques during the 1970s has largely been responsible for detection of cases caused by unusual microorganisms.

In patients with suspected infective endocarditis, the most important laboratory finding is the isolation of bacteria or fungi from at least two or more blood cultures obtained at intervals during a 48 hour period. During the 1940s, studies performed by Beeson et al. (21) demonstrated that bacteremias associated with infective endocarditis are usually continuous. During the 1960s, Werner et al. (22) reported that if any blood cultures are positive in patients with infective endocarditis, most of the other cultures drawn will also be positive. Studies performed during the 1930s and later (17,22,23) indicated that the order of magnitude of bacteremia in patients with infective endocarditis is usually relatively low. In 83% of cases, the quantitative blood cultures contained less than 100 colonies/ml. In 1925, Wright (24) was unable to document an association of bacteremia with fever in patients with infective endocarditis. These early studies and subsequent studies have shown that cultures of peripheral venous blood are as likely to be positive as those of arterial blood (21,24).

How many cultures are necessary? In 1956, Belli and Waisbren (25) reported that 52 of 82 cases of infective endocarditis were diagnosed from the first blood culture and in only 6 cases were more than five blood cultures necessary. More than 10 years later, Werner et al. (22) confirmed this

observation. They reported that streptococci were isolated from the first blood culture in 96% of cases and from one of the first two blood cultures in 98% of cases. Staphylococci were isolated from the first culture in 90% of cases and from one of the first two cultures in 100% of cases. Antimicrobial therapy administered within 2 weeks before blood cultures were obtained reduced the frequency of positive cultures in cases of streptococcal endocarditis from 97 to 91% ($p < 0.002$) (22). In cases of endocarditis caused by microorganisms other than streptococci or staphylococci, the causative agent was isolated from the first blood culture in 82% of cases and from one of the first two blood cultures in 100% of cases (22).

From these studies, it is apparent that blood culture systems available for use in the 1950s were able to diagnose the majority of cases of infective endocarditis and that improvements in microbiologic techniques have permitted detection of cases caused by unusual microorganisms. These earlier studies confirm recent observations that it is rarely necessary to obtain more than three separate sets of blood cultures within a 24 hour period in 2 consecutive days in patients with suspected infective endocarditis.

Clinical Presentation

Prolonged duration of infection before diagnosis due to partial treatment. The classic manifestations of patients with streptococcal and staphylococcal endocarditis, such as peripheral hypersensitivity, embolic phenomena and splenomegaly, have not changed appreciably since the 1950s. Other features of infective endocarditis are quite different in patients seen today compared with those seen 25 years ago. For example, the outpatient use of broad spectrum, orally administered antimicrobial agents has resulted in an increased frequency of partially treated cases of infective endocarditis. As a consequence, the duration of illness before its diagnosis in patients with streptococcal endocarditis is often prolonged. In our experience, 25 to 30% of patients with viridans streptococcal or enterococcal endocarditis have symptoms of infection for 3 months or longer before diagnosis. This prolonged period may increase complications of infective endocarditis, such as valvular dysfunction and large systemic peripheral emboli.

Role of prosthetic valves. Cardiac valve replacement and the use of other intravascular prostheses have increased dramatically during the last 25 years. The clinical presentation of today's patient with endocarditis associated with an intracardiac prosthesis differs from that of the 1950s' patient with endocarditis. Today's patient frequently does not present with the classic manifestations of infective endocarditis. Fever, relapsing bacteremia, congestive heart failure and systemic embolization are more common than manifestations of peripheral hypersensitivity, splenomegaly and a new regurgitant murmur.

Endocarditis in drug addicts. A third major difference between the presentation of today's patients with infective endocarditis and that 25 years ago is associated with illicit intravenous drug abuse. Infective endocarditis in drug addicts frequently involves the tricuspid valve and is often caused by Candida, other fungi or gram-negative bacilli, such as *Pseudomonas* or *Serratia*. Moreover, infections are frequently polymicrobial. Patients with right-sided endocarditis or endocarditis caused by previously unusual gram-negative bacilli often do not present with the manifestations of endocarditis seen in patients with streptococcal or staphylococcal infection. Additionally, these patients frequently leave the hospital before completion of antimicrobial therapy or resume drug abuse after dismissal, and multiple episodes of infective endocarditis are common. These features of infective endocarditis were distinctly uncommon in patients during the 1950s.

Antimicrobial Therapy

Two versus four week treatment regimen. The antimicrobial therapy of patients with viridans streptococcal, enterococcal or staphylococcal endocarditis has not changed appreciably in the last 25 years. During this time, many authorities believed that patients with viridans streptococcal endocarditis should be treated for 4 weeks with penicillin G administered alone or in combination with streptomycin for the first 2 weeks of therapy (25–29). In the late 1950s, Geraci and Martin (30–32) and Tompsett et al. (33) suggested that these patients could be treated successfully for 2 weeks with a combination of penicillin and streptomycin. The short-term regimen did not gain wide acceptance until the late 1970s and early 1980s. Additional published studies substantiated the earlier observations and the 2 week regimen is now accepted as equivalent to a 4 week regimen for the treatment of most patients with penicillin-sensitive viridans streptococcal endocarditis (34–36). The 2 week regimen is safe and effective for the majority of these patients and is more cost effective than are the 4 week regimens.

Streptomycin-resistant enterococcal endocarditis. During the 1940s and 1950s, it was recognized that enterococci are inhibited but not killed by penicillin G alone. Penicillin combined with an aminoglycoside is necessary for bactericidal activity against enterococci. For 25 years, penicillin G and streptomycin administered for 4 to 6 weeks was the standard form of therapy for patients with enterococcal endocarditis (37–39). In the early 1970s, it became known that approximately one-third of streptococci exhibit high level resistance in vitro to streptomycin. These enterococci are not killed synergistically by the combination of penicillin and streptomycin. Penicillin together with gentamicin exerts a bactericidal synergistic effect against these microorganisms. Most authorities now believe that patients with streptomycin-resistant enterococcal endocarditis should

be treated with a combination of penicillin and gentamicin for 4 to 6 weeks (40,41).

Staphylococcal endocarditis. During the 1940s and early 1950s, the majority of isolates of *Staphylococcal aureus* were susceptible to penicillin. Now, virtually all isolates of *S. aureus* produce beta lactamase and are resistant to penicillin G. Methicillin was introduced during the 1950s and the use of semisynthetic beta lactamase-resistant penicillins is now widely accepted as standard antimicrobial therapy for patients with *S. aureus* endocarditis. Use of methicillin may be associated with nephritis, and many authorities now consider methicillin of historic interest. Nafcillin, oxacillin, vancomycin and the cephalosporins have replaced methicillin for the treatment of patients with staphylococcal endocarditis. Endocarditis caused by *Staphylococcal epidermidis* was uncommon during the 1950s. However, because of the increased use of intravascular prostheses, endocarditis caused by this microorganism is now relatively common. During the last 25 years, the majority of strains of *S. epidermidis* have acquired resistance to methicillin, and a combination of vancomycin, rifampin and possibly gentamicin is now considered optimal therapy for patients with endocarditis caused by *S. epidermidis*.

Gram-negative bacillary endocarditis. The antimicrobial therapy for patients with endocarditis caused by gram-negative bacilli has also changed dramatically in the last 25 years with the introduction of aminoglycosides, such as gentamicin and amikacin and broad spectrum cephalosporins. Bactericidal therapy for patients with gram-negative endocarditis was not available during the 1950s. As discussed later, advances in the technique of cardiac valve replacement have greatly improved the prognosis of patients with gram-negative bacillary endocarditis and endocarditis from other causes.

Echocardiography

In the past decade, the development of echocardiography has had a significant impact on the diagnosis and management of infective endocarditis. The value of echocardiography in the evaluation of functional cardiac anatomy and cardiac disease was first reported by Edler and Hertz (42). Dillon et al. (43) were the first to report the value of M-mode echocardiography in the diagnosis of bacterial endocarditis. Their study included eight patients, five with vegetative lesions involving the aortic valve and three with lesions on the mitral valve, all proved at the time of surgery or autopsy. From this study, they concluded that vegetations of 2 mm or greater could be identified using M-mode echocardiography. Four of their patients with endocarditis had negative blood cultures. Although they stated that there does not seem to be any problem in confusing the echocardiographic signs of vegetation with the usual findings of a thickened mitral or aortic valve, they did note that there conceivably might be some confusion between the echocardiograms of patients with vegetation and those with myxomatous degeneration. Subsequent investigators (44–48) have also recognized and reported on the usefulness of M-mode echocardiography in the evaluation of the patient with endocarditis.

Two-dimensional echocardiography is superior to M-mode echocardiography in patients with infective endocarditis and is particularly useful in patients with prosthetic valves and those with tricupsid valve endocarditis (49–52). It is superior also in identifying the complications of endocarditis, including intramyocardial abscesses and disruption of valvular tissue and valvular supporting tissue.

Diagnostic accuracy. The diagnostic value of echocardiography depends primarily on the demonstration of vegetations (Fig. 1 to 3). Various attempts have been made to estimate the sensitivity, specificity and diagnostic accuracy of this technique, based on the presence or absence of vegetation on cardiac valves (47,48,51–54). The reported prevalence of vegetation detected by echocardiography in patients with infective endocarditis has ranged from 13 to 78% (53–55).

The frequency with which macroscopic vegetations occur in cases of active infective endocarditis must also be considered. Autopsy studies have shown that vegetations occur in 53% of patients who die of active infective endocarditis (56,57). These autopsy cases obviously include patients who experienced the lethal complications of vegetative endocarditis. All complications are known to occur more frequently in patients with vegetations then in those without. Therefore, the frequency with which vegetations are detected echocardiographically may be less than 53%.

Limitations. If the study is performed in patients with proved active endocarditis, then the sensitivity, specificity and diagnostic accuracy of echocardiography will be improved; however, the diagnostic value of the study will be limited. Further, if the clinical diagnosis of infective endocarditis is known, then interpretation of the echocardiographic findings may be biased toward the diagnosis of vegetations (47,54).

The ultrasonic characteristics of a vegetation affect its echocardiographic detection. It is likely that some vegetations will have the same acoustical properties as the surrounding tissue and therefore go undetected. The size of the vegetation is equally important. Thompson et al. (53) reported the detection of lesions as small as 1 mm, but these lesions were calcified and a vegetation in its early state rarely contains calcium. It is unlikely then that vegetations smaller than 2 mm will be identified given the present resolution characteristics of current echocardiographic equipment. The instrument used and the skill of the echocardiographic technician are additional factors to be considered (50). The best results are obtained by combining the M-mode and two-dimensional techniques.

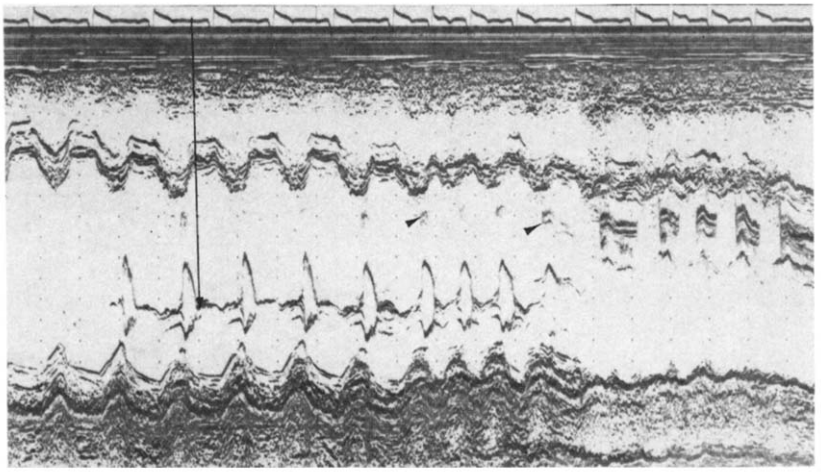


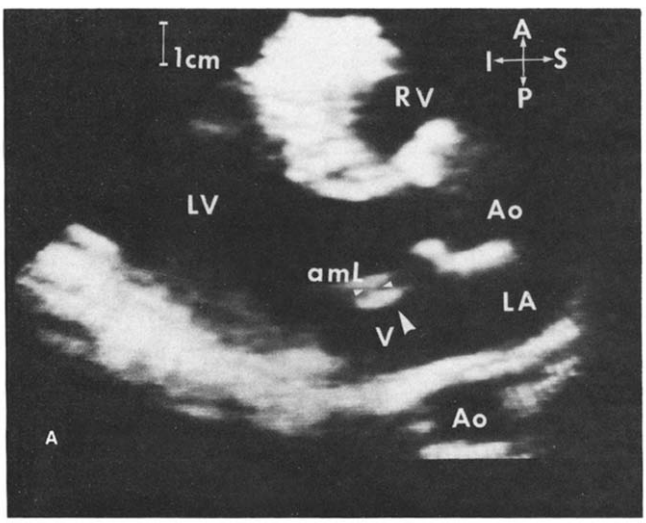
Figure 1. Apex to base scan of a 36 year old man with infective endocarditis involving a bicuspid aortic valve. Note the enlarged left ventricular chamber **(left)** with dynamic wall motion, premature closure of the mitral valve **(long vertical arrow),** the abnormal diastolic echoes in the left ventricular outflow tract (identified by small **arrowheads**), the abnormal echoes in the aortic root seen during diastole (secondary to vegetation) and the enlarged left atrium **(right)**. (Reprinted with permission from Giuliani ER. Role of echocardiographic studies in the ambulatory patient. Cardiovasc Clin 1980;10:109.)

The patient plays a critical role in enhancing the effectiveness of echocardiography. In the young patient who is easily studied, a complete examination can be obtained in most cases. However, in patients who are elderly, obese or postoperative, or have chronic obstructive pulmonary disease or chest deformities, a complete ultrasonic cardiac examination is not possible. In these patients the frequency of identification of vegetations will be smaller.

Preexisting valvular disease adds to the difficulty of the examination. If the patient has underlying rheumatic valvular heart disease, it becomes difficult and often impossible to differentiate vegetative lesions from the chronic underlying pathologic process. Many workers now have reported on the difficulty of diagnosing endocarditis in patients who have myxomatous valvular changes, particularly of the mitral valve.

Patients who have had previous endocarditis also pose a problem. Patients with echocardiographically demonstrable vegetations are often cured of their infections. Experience has shown that although many of these vegetations disappear, some persist and either become smaller or remain the same size as judged by echocardiography.

Finally, the timing of the echocardiographic examination in relation to the onset of the illness should be considered (55). Although the minimal length of time required to de-



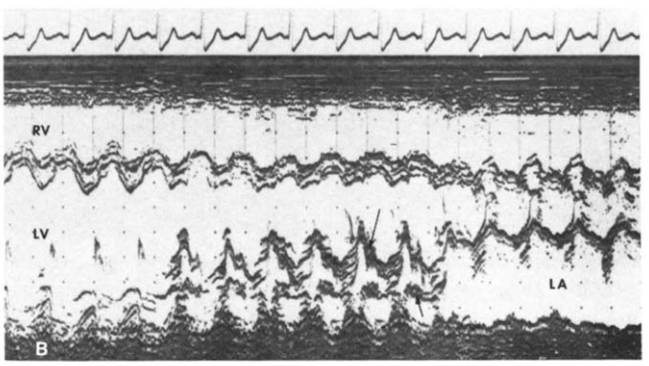


Figure 2. A, Still frame of the left side of the heart on its long axis demonstrating vegetations attached to the atrial surface of the anterior mitral leaflet **(large arrowhead,** V). Note point of attachment of the vegetation **(small arrowheads)**. aml = anterior mitral leaflet; Ao = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle. In each illustration the depth markings are given in centimeters. Arrow direction: A = anteriorly; I = inferiorly; P = posteriorly; S = superiorly. **B,** M-mode scan from apex to base of the heart of a patient with infective endocarditis involving the mitral valve. Note shaggy echoes encompassing the anterior and posterior mitral leaflets **(arrows)**, both of which retained their normal motion pattern. The left ventricle (LV) is dilated with good ventricular function. The left atrium (LA) is enlarged. The electrocardiogram at the top of the tracing is for reference. RV = right ventricle. (Reprinted from Giuliani ER, Nasser FN [73], with permission.)

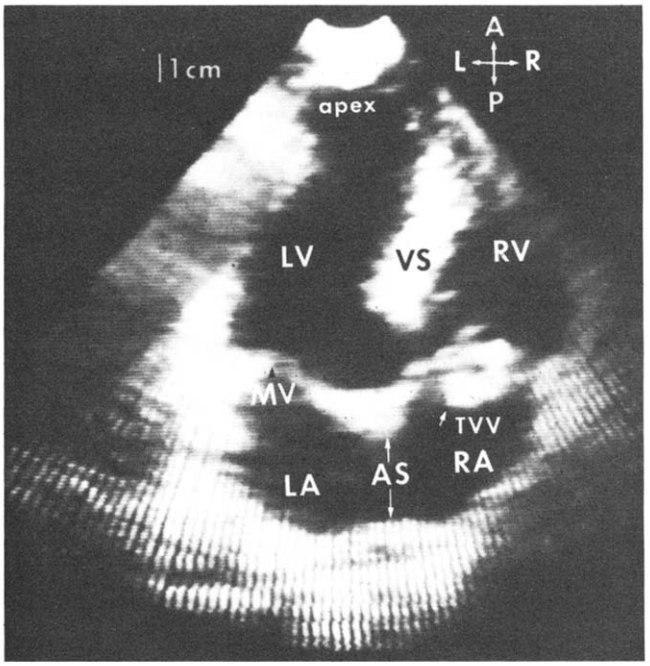


Figure 3. Still frame of a four chamber view from the apical position demonstrating tricuspid valve vegetation (**small arrow,** TVV). After this study, the patient had a pulmonary embolus. Subsequent echocardiographic studies demonstrated a marked reduction in the size of the vegetation. AS = atrial septum; MV = mitral valve; VS = ventricular septum. Arrow direction: L = left; R = right; other lettering as in Figure 2A.

velop an identifiable lesion by echocardiography is unknown, studies have shown that a vegetation identifiable by echocardiography is larger in patients with a longer duration of symptoms than in those with a shorter duration of symptoms (58,59).

Despite these limitations, it is important to identify vegetations. The patients with active endocarditis in whom valvular vegetations are detected represent a subset of patients whose clinical course is quite different from that of patients who do not manifest this finding. Patients with demonstrable vegetations have a higher rate of all complications.

Valvular Incompetence

If valvular tissue is destroyed or supporting structures are disrupted as a result of active endocarditis, the hemodynamic consequence is valvular incompetence. The rate and extent of tissue destruction will determine the severity of valvular incompetence and the clinical course of the patient. Patients tolerate incompetence of the right cardiac valves quite well. The regurgitation that develops when left cardiac valves are affected, particularly aortic valve incompetence, is tolerated less well.

Aortic Valve Incompetence

Wray (46) described the diagnostic echocardiographic criteria for disruption of the aortic valve, and these findings can be demonstrated by both M-mode and two-dimensional echocardiography. Pridie et al. (60) were the first to show the importance of echocardiographic determination of early mitral valve closure in patients with acute aortic incompetence (Fig. 1). Others (47,61,62) have confirmed this finding. Some workers believe that by itself the finding is an indication for surgical intervention. Our experience supports this opinion because our patients who demonstrated premature mitral valve closure either were in a clinically unstable condition or had refractory congestive heart failure and, therefore, were candidates for aortic valve replacement. Thus, in selected patients with aortic involvement, the echocardiogram reflects the severity of the aortic valve incompetence.

In the patient who is cured of active endocarditis but still has chronic aortic valve incompetence, the echocardiogram is useful because its data may be of prognostic value (63). We have confirmed the findings of others that the M-mode left ventriculogram is useful in predicting patient outcome after replacement of the aortic valve (64). Patients who demonstrate a change in left ventricular dimension greater than 35% have a better prognosis than do patients whose dimensional change is 30% or less (Fig. 4).

Mitral Valve Incompetence

Acute mitral valve incompetence due to active endocarditis is most frequently caused by rupture of one or more chordae tendineae to the mitral valve leaflets. Two-dimensional echocardiography has allowed the documentation of this clinical event (65), and can further support the clinical diagnosis (66,67). Fortunately, many patients tolerate the insult of acute mitral incompetence quite well and their course is like that of any patient with nonrheumatic mitral valve incompetence. In this group of patients with chronic mitral incompetence, serial echocardiographic examinations have proved helpful in predicting which patients will do well after mitral valve repair or replacement.

We studied 96 patients who had surgery for chronic mitral valve incompetence. In this group, there was a higher 5 year mortality rate in patients with a left ventricular internal systolic dimension ($LVID_s$) of more than 50 mm or a change in diameter of less than 31% (Fig. 5). Atrial fibrillation, which was related to larger left atrial dimensions, was also associated with a poorer prognosis (68).

Myocardial Abscesses

The frequency of complication of myocardial abscesses is unknown. Arnett and Roberts (69) reported 22 aortic ring abscesses and 2 mitral ring abscesses in 74 patients who died with infective endocarditis. A similar observation was reported by Burnside and DeSanctis (70). Aortic ring abscesses (Fig. 6 and 7) are detected more frequently by echocardiography than are abscesses of the mitral ring. Although these abscesses have been identified using the M-mode tech-

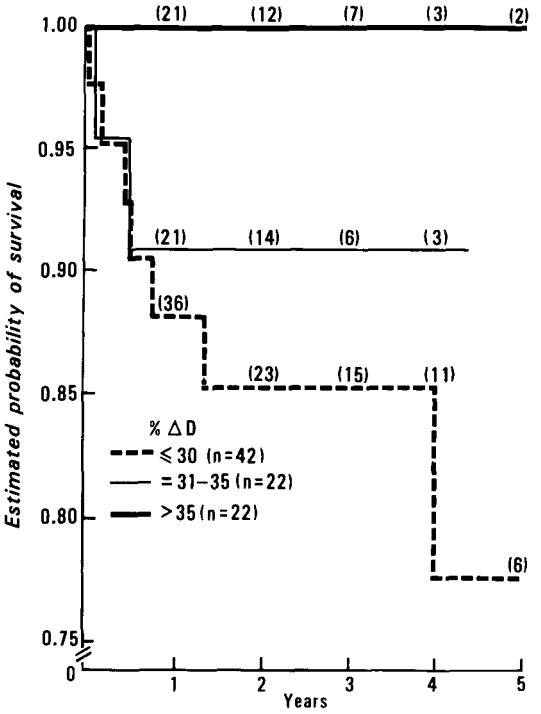


Figure 4. Relation between probability of survival after valve replacement for aortic insufficiency and preoperative percent change in left ventricular dimension (%ΔD). Patients with low values (<30%) have a significantly decreased probability of survival ($p<0.05$). Numbers in parentheses are numbers of patients. (Reprinted from Cunha CLP, Giuliani ER, Fuster V, et al. [64], with permission.)

nique (71), the two-dimensional technique is far superior (72,73). Nakamura et al. (74) were the first to report the echocardiographic appearance of mitral ring abscesses. We have seen complications of intramyocardial abscess develop in patients with involvement of the aortic, mitral and tricuspid valves. This complication is found in about 10% of our patients who have demonstrable valvular vegetations. In our opinion, the demonstration of this complication is not an indication for immediate surgical intervention; the indications depend on the patient's clinical course, specifically the status of the cardiovascular system.

Embolization

Finally, a major complication associated with endocarditis is embolization. Although embolization occurs in patients with or without demonstrable vegetation, its incidence is significantly greater in patients with vegetation (55,58). In our experience, embolization occurs in approximately one-third of patients with proved bacterial endocarditis and echocardiographically demonstrated vegetations involving the left-sided cardiac valves. Embolization is more frequent if vegetations involve the aortic valve as compared with the mitral valve. Because of the large incidence of systemic emboli, frequently to the cerebrovascular system, some physicians recommend cardiac surgery with valve replacement in patients who have vegetation. In our opinion, the presence of vegetation is not necessarily an indication for surgical intervention (75). The patient with infective endocarditis and demonstrable vegetation presents a difficult management problem that requires an individualized clinical decision.

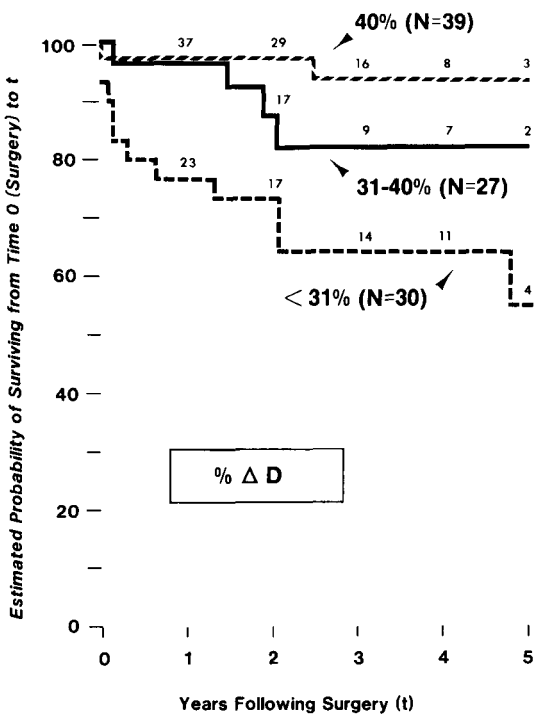
Clinical Application

The application of echocardiography to patients with active endocarditis has provided a better understanding of the natural course of the disease, enabled us to identify accurately the complications of active infective endocarditis and permitted us to separate a subset of patients at high risk of complications and death. In patients cured of endocarditis but with chronic valvular incompetence, the echocardiogram contains data of prognostic value that may be helpful in timing surgical intervention. The echocardiographic examination aids but does not allow the diagnosis of active endocarditis, and should be used in combination with other factors to determine the need for surgical therapy. The data obtained by echocardiography, if integrated with the clinical data and other laboratory data, can be and have been very useful in the care of patients with infective endocarditis.

Indications for Cardiac Surgery

Congestive heart failure. Although infective endocarditis is primarily managed with medical therapy, cardiac surgery has played an important role in the past 12 to 15 years. Cardiac valve replacement has been lifesaving in

Figure 5. Relation between the probability of survival after valve replacement for mitral insufficiency and preoperative percent change of left ventricular dimension (%ΔD). Patients with low values have a significantly decreased probability of survival. Small numbers indicate numbers of patients.



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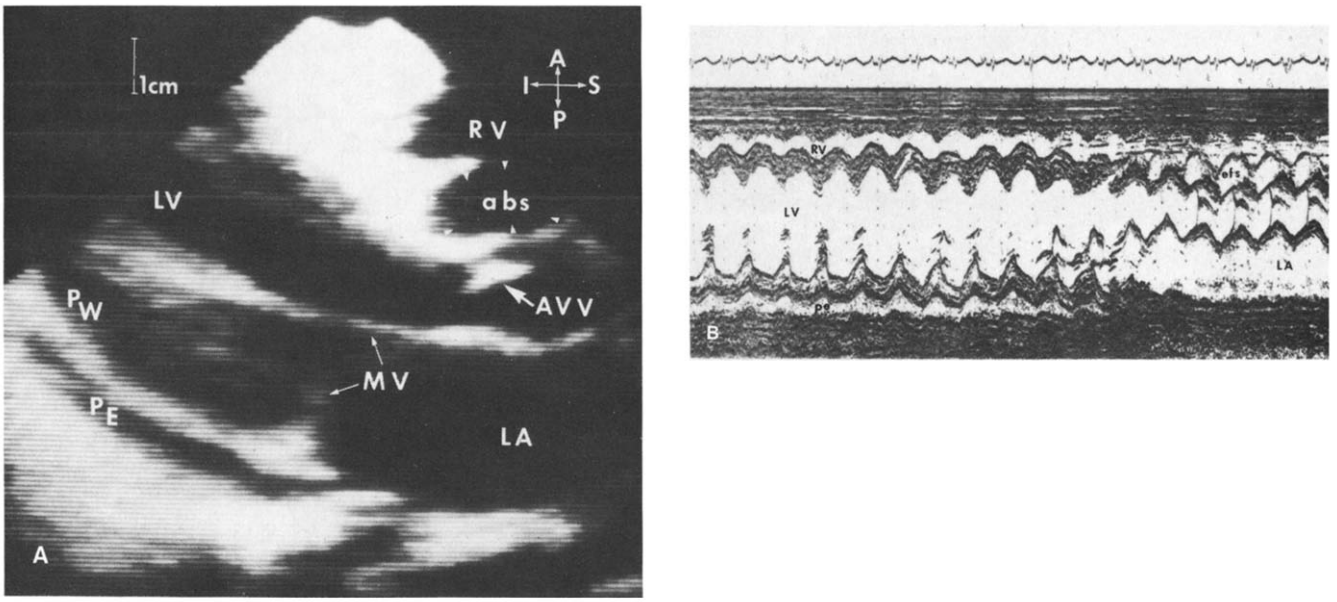

Figure 6. A, Still frame of the long axis view of the left ventricle (LV) in a patient who had infective endocarditis involving the aortic valve and developed an aortic root abscess that dissected from the anterior root down into the interventricular septum (abs, **small arrows**). AVV, **arrow** = aortic valve vegetation; MV = mitral valve; PE = pericardial effusion; PW = posterior wall; other abbreviations as in Figure 2A. **B,** M-mode scan from apex to base of left ventricle in the same patient. Note the echo-free space (efs) representing an aortic root abscess. Also note the thickened aortic leaflet echoes in diastole, the dilated left ventricle (LV) with good systolic function and the small pericardial effusion (pe). Other abbreviations as in Figure 2B. (Reprinted with permission from Nasser FN, Giuliani ER. Clinical Two-Dimensional Echocardiography. Chicago: Year Book Medical, 1982.)

selected patients with infective endocarditis. This is particularly true in patients with intractable heart failure due to destruction of valve tissue or its supporting structures (76–83).

Congestive heart failure is the leading cause of death among patients with infective endocarditis (17,84–87). With this complication, the mortality rate is higher in patients with aortic infective endocarditis (40 to 93%) than in those with mitral infective endocarditis (17 to 66%) (76). Among patients with severe congestive heart failure complicating infective endocarditis, the mortality rate is higher in those treated medically than in those given medical therapy plus cardiac valve replacement (76,77,88–91).

The indications for cardiac surgery in patients with infective endocarditis are similar to those for patients with valvular heart disease from other causes. An analysis of patients who underwent cardiac valve replacement because of heart failure due to infective endocarditis disclosed that the operative mortality was closely related to the degree of functional heart failure at the time of operation (92). The overall mortality rate was higher in patients with class IV disability (17%) than in patients with class III (7%) or II (8%) disability, although the difference was not statistically significant. The mortality rate for patients with class IV disability who had undergone aortic valve replacement was significantly higher (22%) than that for patients with class III (0) or II disability (6%, $p = 0.01$) (92). The operative mortality rate was similar to that of patients without infective endocarditis when the degree of heart failure was the same at the time of operation.

In patients with severe class IV heart failure or with sudden onset of severe aortic valve incompetence due to infective endocarditis, prompt cardiac valve replacement offers the best hope of survival. This operation can be performed successfully in patients with active infection, even when blood cultures are positive in the immediate preoperative period (93). In this type of patient, delay to stabilize the heart failure with medical treatment or to complete a course of antimicrobial therapy commonly results in death from heart failure (93). The hemodynamic status of patients with infective endocarditis, rather than the activity of the infection or the length of preoperative antimicrobial therapy, should be the determining factor in the timing of cardiac valve replacement.

Embolism. An infrequent, but important, additional group of complications warrants surgical consideration in selected cases. Echocardiography has played an important role in suggesting a need for surgical intervention. The greatest frequency of major embolic events occurs in association with infections that produce large mobile vegetations, such as *Haemophilus parainfluenzae* and other slow-growing gram-negative bacilli, fungi (especially *aspergillus*) and nutritionally variant viridans streptococci (94,95). Patients with no history of emboli or only a single embolic event who have large valvular vegetations on the two-dimensional echocardiogram are worrisome, but these conditions by them-

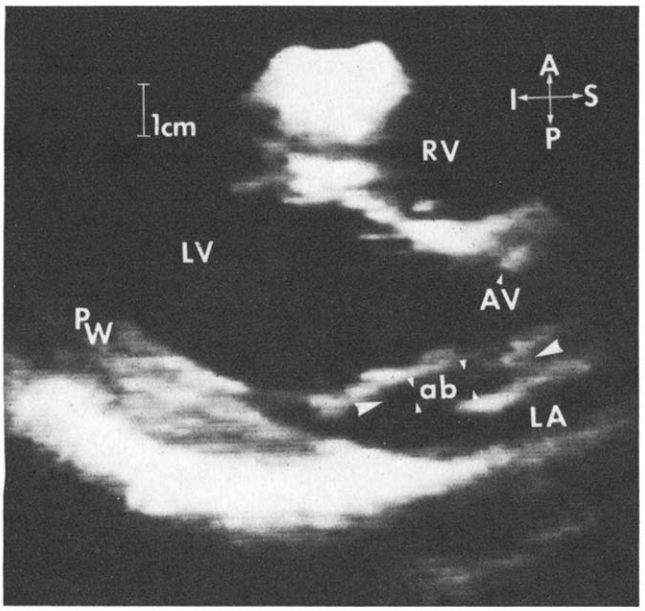

Figure 7. Still frame of the long axis view of the left side of the heart in a young patient with aortic valve endocarditis whose complication of aortic root abscess involved the posterior aortic root and dissected down into the anterior mitral leaflet **(arrows).** ab = abscess; other abbreviations as in Figure 2A.

selves do not usually seem to justify valve replacement at the present time. If more than one embolic episode has occurred in this circumstance, valve debridement or replacement is recommended by some clinicians (96,97). To date, we have elected to make the decision in this situation on an individual basis, depending on the microbiologic etiology and the presence or absence of large mobile vegetations on subsequent two-dimensional echocardiography after an initial embolic event.

Abscesses. In early experiences with two-dimensional echocardiography, large abscesses in the aortic root or septum that were occasionally encountered raised the question of possible surgical intervention. In most of these patients, the abscess decreased in size and eventually cleared with antibiotic therapy alone.

Fungal endocarditis and relapsing endocarditis. Additional indications for valve replacement are found in patients with fungal endocarditis. Such patients should undergo cardiac valve replacement in combination with antifungal therapy before, during and after operation (98). Staphylococcal infective endocarditis may be cured medically in some patients, but valve replacement is indicated if relapse occurs. Patients with gram-negative bacillary endocarditis may be allowed a second relapse before valve replacement is undertaken, and patients with penicillin-sensitive viridans and enterococcal infective endocarditis have been allowed as many as three relapses before cardiac valve replacement (99–101).

The rare patient who develops an aneurysm of the sinus of Valsalva or atrioventricular junctional tissue will require urgent surgery. A patient with infective endocarditis who develops abrupt right-sided heart failure with a continuous basal murmur should be suspected of having one of these lesions (102).

Purulent pericarditis. This is a rare complication of infective endocarditis. It is usually associated with staphylococcal infective endocarditis, is detectable by two-dimensional echocardiography and requires prompt surgical drainage and antimicrobial therapy. Pericardiectomy is necessary in some patients.

Prosthetic valve endocarditis. Infective endocarditis superimposed on prosthetic valves is difficult to manage. With a sensitive organism and early treatment using appropriate antimicrobial agents, the infection may be eradicated. If the infection persists or relapse occurs, the infected valve should be removed and treatment continued for 3 to 4 weeks (102).

Tricuspid valve endocarditis. Patients with tricuspid valve endocarditis present unique surgical problems. If the infection is resistant to antibiotic agents, as is often true with *Pseudomonas* and other gram-negative bacilli, fungi and some other organisms, excision of the tricuspid valve is the operation of choice. Absence of the tricuspid valve may be well tolerated in patients who do not have pulmonary hypertension (103).

The role of surgery in the management of infective endocarditis has been clarified significantly during the past quarter century, but in individual patients the question of surgical intervention and its timing still may prove troublesome.

Conclusion

Thus, in the past 25 years we have noted impressive advances in the management of patients with infective endocarditis. Improved bacteriologic techniques have allowed the detection of cases of infective endocarditis due to unusual organisms. Bactericidal therapy has become available for patients with gram-negative endocarditis and antimicrobial therapy has improved. Echocardiography has evolved into an important diagnostic and management aid and cardiac valve replacement has dramatically improved the outlook for many patients.

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